
A critical look: Challenges in differentiating human pluripotent stem cells into desired cell types and organoids.

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Public Summary:

A major ambition of regenerative medicine is to generate new human organs and cells in a Petri dish from embryonic stem cells. While substantial progress has been made towards this goal by the entire stem cell field, a number of critical challenges remain. This review article provided an unvarnished view of the remaining challenges and also suggested a number of approaches to overcome those challenges. For instance, new and innovative approaches have been recently devised to convert embryonic stem cells into desired types of cells with increased speed, efficiency and precision, and should see widespread adoption across the field.

Scientific Abstract:

Too many choices can be problematic. This is certainly the case for human pluripotent stem cells (hPSCs): they harbor the potential to differentiate into hundreds of cell types; yet it is highly challenging to exclusively differentiate hPSCs into a single desired cell type. This review focuses on unresolved and fundamental questions regarding hPSC differentiation and critiquing the identity and purity of the resultant cell populations. These are timely issues in view of the fact that hPSC-derived cell populations have or are being transplanted into patients in over 30 ongoing clinical trials. While many in vitro differentiation protocols purport to "mimic development," the exact number and identity of intermediate steps that a pluripotent cell takes to differentiate into a given cell type in vivo remains largely unknown. Consequently, most differentiation efforts inevitably generate a heterogeneous cellular population, as revealed by single-cell RNA-sequencing and other analyses. The presence of unwanted cell types in differentiated hPSC populations does not portend well for transplantation therapies. This provides an impetus to precisely control differentiation to desired ends—for instance, by logically blocking the formation of unwanted cell types or by overexpressing lineage-specifying transcription factors—or by harnessing technologies to selectively purify desired cell types. Conversely, approaches to differentiate three-dimensional "organoids" from hPSCs intentionally generate heterogeneous cell populations. While this is intended to mimic the rich cellular diversity of developing tissues, whether all such organoids are spatially organized in a manner akin to native organs (and thus, whether they fully qualify as organoids) remains to be fully resolved. This article is categorized under: Adult Stem Cells > Tissue Renewal > Regeneration: Stem Cell Differentiation and Reversion Gene Expression > Transcriptional Hierarchies: Cellular Differentiation Early Embryonic Development: Gastrulation and Neurulation.

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